Molecules to Correct Aberrant RNA Signature in Human Diseased Neurons

Grant Award Details

Molecules to Correct Aberrant RNA Signature in Human Diseased Neurons

Grant Type: Early Translational III

Grant Number: TR3-05676

Project Objective: The objective of this DCF project is to identify a small molecule that can reverse the aberrant RNA signature in human iPSC-derived motor neurons from patients with mutations in RNA binding proteins TDP-43 and FUS/TLS, known to cause familial ALS.

Investigator:

Name:	Eugene Yeo
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Amyotrophic Lateral Sclerosis, Neurological Disorders

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,532,323

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	Molecules to Correct Aberrant RNA Signature in Human Diseased Neurons
Public Abstract:	Approximately 5,600 people in the U.S. are diagnosed with ALS each year. The incidence of ALS is two per 100,000 people, and it is estimated that as many as 30,000 Americans may have the disease at any given time. There are no effective therapies of ALS to-date. Recent genetic discoveries have pinpointed mutations that lead to the aberrant function of two proteins that bind to RNA transcripts in neurons. Misregulation of these RNA binding proteins is responsible for the aberrant levels and processing of hundreds of RNA representing genes that are important for neuronal survival and function. In this proposal, we will use neurons generated from patient cells that harbor the mutations in these RNA binding proteins to (1) prioritize a RNA "signature" unique to neurons suffering from the toxic function of these proteins and (2) as an abundant source of raw material to enable high-throughput screens of drug-like compounds that will bypass the mutations in the proteins and "correct" the RNA signature to resemble that of a healthy neuron. If successful, our unconventional approach that uses hundreds of parallel measurements of specific RNA events, will identify drugs that will treat ALS patients.
Statement of Benefit to California:	Our research aims to develop drug-like compounds that are aimed to treat Amyotrophic Lateral Sclerosis (ALS), which may be applicable to other neurological diseases that heavily impact Californians, such as Frontotemporal Lobar Degeneration, Parkinson's and Alzheimer's. The cellular resources and genomic assays that we are developing in this research will have great potential for future research and can be applied to other disease areas. The cells, in particular will be beneficial to California health care patients, pharmaceutical and biotechnology industries in terms of improved human models for drug discovery and toxicology testing. Our improved knowledge base will support our efforts as well as other Californian researchers to study stem cell models of neurological disease and design new diagnostics and treatments, thereby maintaining California's position as a leader in clinical research.